

(19)



Europäisches Patentamt

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Office européen des brevets



(11)

**EP 0 832 649 B1**

(12)

## EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention  
of the grant of the patent:

**12.09.2001 Bulletin 2001/37**

(51) Int Cl.7: **A61K 31/415**, A61K 31/14,  
A61K 31/47

(21) Application number: **96916340.1**

(86) International application number:  
**PCT/JP96/01553**

(22) Date of filing: **07.06.1996**

(87) International publication number:  
**WO 96/40121 (19.12.1996 Gazette 1996/55)**

(54) **ANTIFUNGAL AGENT**

FUNGIZID

AGENT ANTIFONGIQUE

(84) Designated Contracting States:

**AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC  
NL PT SE**

(56) References cited:

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<b>JP-A- 1 066 121</b>	<b>US-A- 5 143 917</b>

(30) Priority: **07.06.1995 JP 14059895**

(43) Date of publication of application:  
**01.04.1998 Bulletin 1998/14**

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**EP 0 832 649 B1**

## Description

[0001] This invention relates to an antifungal composition. More particularly, it is concerned with an antifungal composition wherein an imidazole-type antifungal compound (bifonazole, miconazole nitrate) is combined with a quaternary ammonium salt (dequalinium chloride).

[0002] Imidazole-type antifungal compounds as a worldwide, leading antifungal agent are those having an imidazole group in the chemical structure thereof. They have been believed to exhibit an antifungal activity mainly by damaging the cell membrane of fungi.

[0003] For those imidazole-type antifungal agents, there have been suggested as an active ingredient for Switch OTC drugs clotrimazole, miconazole nitrate, econazole nitrate, bifonazole, oxiconazole nitrate, sulconazole nitrate, tioconazole and the like.

[0004] Clotrimazole has been applied as external preparations solely and is effective against Trichophyton and also Candida. If applied to the healthy skin, *in vivo* absorption of the agent can hardly be observed, while local side-effects such as irritating feeling, flare, anthema and the like in the skin are believed to be manifested, which a direct irritating effect on the skin or allergic effect is believed to participate in.

[0005] Bifonazole exhibits a similar action to that of clotrimazole and is effective for many human pathogenic fungi. It is said that this agent possesses a more excellent skin permeability by external use and a higher drug retention in the cutaneous tissues as compared with other imidazole-type antifungal agents. As is similarly seen with clotrimazole, local side-effects such as irritating feeling, flare, anthema and the like in the skin are manifested.

[0006] Miconazole nitrate and econazole nitrate exert an antifungal activity against Trichophyton, Candida, Aspergillus, Cryptococcus and others. When applied to the healthy skin, *in vivo* absorption of these agents can hardly be observed, while similar local side-effects to those of clotrimazole are observed and a very few systemic side-effects are observed, when applied externally in a conventional manner.

[0007] The term "a quaternary ammonium salt" as used herein refers to dequalinium chloride.

[0008] It has been supposed that the cation released from the quaternary ammonium salt might be adsorbed on the microbial surface and then carried into the cells to affect the cellular proteins, whereby an antifungal activity could be exerted.

[0009] Dequalinium chloride has been reported to exert an antimicrobial activity against bacteria (especially, Staphylococcus aureus and hemolytic streptococci) and fungi. It has been dispensed mainly for buccal antifungal agents or antiodontalgic and antipyrorrheal agents.

[0010] Although there has not yet been reported a medicament wherein an imidazole-type antifungal compound is blended or combined with a quaternary ammonium salt, U.K. Patent No. 2 208 598A discloses a combination of an imidazole-type antifungal compound with salicylic acid or benzoic acid.

[0011] Medline Abstract no. 91049213, S.A. Pavlenko 1991: "Otomycoses in the Kuznetsk Region and Organisation of Medical Services for this Group of Population"; Russian article in Vestnik Otorinolaringologii, vol. 4, 1990, pages 70-74 discloses a combination of clotrimazole with dequalinium chloride, but it neither discloses nor suggests a combination of miconazole nitrate or bifonazole with dequalinium chloride.

[0012] US-A-5 143 917 (Medice Chem.-Pharm. Fabrik Putter GmbH & Co KG) discloses a combination of miconazole with benzethonium chloride. Also, it enumerates benzalkonium chloride and dequalinium acetate, but any specific combination thereof is not described therein. No specific description on dequalinium chloride is made, and it neither discloses nor suggests that a pharmaceutical composition comprising dequalinium chloride would give a safe pharmaceutical preparation without any skin-irritating property.

[0013] Japanese Patent Abstract no. 05 238 908 (Teisan Seiyaku KK) discloses a combination of clotrimazole with benzalkonium chloride.

[0014] Derwent Abstract no. 90-247139 & CN-A-1 036 902 (Microbe Epidemic Di) discloses an anti-ringworm composition which comprises a combination of an imidazole derivative with a tetra-ammonium salt.

[0015] BE-A-768 808 (N.V. Koninklijke Pharmaceutische Fabrieken v/h Brocades-Stheeman & Pharmacia) discloses a composition against Candida which comprises a combination of an imidazole derivative with a quaternary ammonium salt.

[0016] Treatment of athlete's foot, radical cure of which is generally said to be difficult, requires continuous application of a medicament over a prolonged period of time. The symptom of athlete's foot appears suppressed in the winter season, but this never means complete cure of the disease but simply a slowdown of the fungal activity. Thus, there has been desired a development of a medicament having a higher therapeutic effect. Moreover, it is difficult to discriminate whether pathogenesis of athlete's foot may be caused by Trichophyton or Candida, and it can be done only by means of a microscopic examination by a medical specialist or the cultivation of a pathogenic microbe. Therefore, a medicament which is effective against both of those pathogenic fungi is important. Furthermore, the imidazole-type antifungal compounds may show, as mentioned above, local side-effects such as irritating feeling, flare, anthema and the like in the skin. There may be required any inventive means to cause no side-effects by reducing an amount of

said compound to be blended.

**[0017]** We have conducted various screenings in order to select an agent capable of effectively acting together with the imidazole-type antifungal compound and having an antifungal activity against both *Trichophyton* and *Candida* and in order to improve the feeling in use thereof. Now, we have found that a certain quaternary ammonium salt has a synergistically potentiating effect on an antifungal activity, on the basis of which this invention has been completed.

**[0018]** More specifically, this invention is directed to an antifungal composition comprising (A) miconazole nitrate or bifonazole and (B) dequalinium chloride for use as a medicament acting against fungi of *Trichophyton* and *Candida*. Moreover, the invention relates to the use of a composition which comprises (A) miconazole nitrate or bifonazole and (B) dequalinium chloride for the manufacture of a medicament acting against fungi of *Trichophyton* and *Candida*.

**[0019]** An amount of the miconazole nitrate or bifonazole to be blended is 0.2 - 1% by weight, preferably 0.5 - 1% by weight.

**[0020]** An amount of dequalinium chloride to be blended is 0.1 - 1% by weight, preferably 0.5 - 1% by weight.

**[0021]** It is preferably blended at 0.1 - 1 part by weight, more preferably 0.1 - 0.5 part by weight, per 1 part by weight of the imidazole-type antifungal compound.

**[0022]** The active ingredient of this invention may be formulated to external preparations such as solutions, lotions, emulsions, tinctures, ointments, creams, aqueous gels, oily gels, aerosols and the like, by blending known additives, if necessary, according to a conventional method.

**[0023]** For aqueous components, there may be mentioned propylene glycol, 1,3-butylene glycol, glycerol, ethanol, macrogols and the like.

**[0024]** For oily components, there may be mentioned diisopropyl adipate, stearyl alcohol, cetyl alcohol, squalene, medium chain fatty acid triglycerides and the like.

**[0025]** As polymers, there may be mentioned a carboxyvinyl polymer, methyl cellulose and the like.

**[0026]** As pH adjustors, there may be mentioned citric acid, inorganic bases such as sodium hydroxide and the like, organic amines such as diisopropanolamine and the like, and others.

**[0027]** As antioxidants, there may be mentioned dibutyl hydroxytoluene (BHT), butyl hydroxyanisole (BHA),  $\alpha$ -tocopherol, erythorbic acid, sodium pyrosulfite and the like.

**[0028]** As coloring agents, there may be mentioned titanium oxide and the like.

**[0029]** As surfactants, there may be mentioned polyoxyethylene hardened castor oil, sorbitan monostearate, sorbitan monopalmitate, monostearic acid glycerides, sorbitan monolaurate, polyoxyethylene-polyoxypropylene block copolymer, polysorbates, sodium lauryl sulfate, sucrose fatty acid esters, lecithin and the like.

**[0030]** As stabilizers, there may be mentioned EDTA-2Na and the like.

**[0031]** More specifically, those quaternary ammonium salts, the synergistic antifungal effect of which had been established, were further examined on their skin irritating property, their formulation to pharmaceutical preparations and others, and, as a result, it has been found that dequalinium chloride is most preferred as shown in Table 1.

Table 1

Name of compound	Adaptability as pharmaceutical preparation	Skin irritating property
Benzalkonium chloride (comparative compound)	○	△
Dequalinium chloride	○	○

**[0032]** In the present invention, an effective amount of miconazole nitrate to be blended is 0.2 - 1% by weight, preferably 0.5 - 1% by weight.

**[0033]** An effective amount of dequalinium chloride to be blended is 0.05 - 0.5% by weight, preferably 0.1 - 0.5% by weight.

**[0034]** Dequalinium chloride is used at 0.1 - 1 part by weight, preferably 0.1 - 0.5 part by weight, per 1 part by weight of miconazole nitrate.

**[0035]** The pharmaceutical composition of this invention is a very potent antifungal agent with a potentiated antifungal activity.

**[0036]** The effect of this invention will be illustrated by the following examples.

#### Test Example 1

##### (1) Test strains

**[0037]** The following microorganisms were used as test strains:

Trichophyton rubrum  
Trichophyton mentagrophytes

(2) Preparation of spore suspension

[0038] The test strain was inoculated onto a slant in a test tube containing 1/10 Sabouraud's agar medium and cultivation was conducted at 28°C for 3 - 4 weeks. After completion of the cultivation, the mycelia were collected by scratching with a sterile spatula and transferred into an Erlenmeyer flask (100 ml volume) containing sterilized glass beads and 10 ml of physiological saline containing 0.1% Tween 80 and then shaken for one hour. Then, the mixture was filtered through cotton plug to give a spore suspension. The spore suspension was stored under refrigeration and used within one month.

(Composition of 1/10 Sabouraud's agar medium)

[0039] Glucose 4.0 g, peptone 1.0 g, potassium dihydrogenphosphate (anhydrous) 1.5 g, magnesium sulfate (heptahydrate) 1.0 g, sodium nitrate 1.0 g, agar 20.0 g, distilled water 1000 ml

(3) Preparation of test compositions

[0040] Test compositions were prepared by using miconazole nitrate and benzalkonium chloride, dequalinium chloride, benzethonium chloride or salicylic acid, dissolving them and then preparing doubling dilutions with DMSO as a dilution solvent so as to correspond to the test concentrations. Benzalkonium chloride, benzethonium chloride and salicylic acid were tested for comparative purposes.

(4) Test procedure

[0041] The diluted composition and Sabouraud's agar medium (Eiken Chemical Co., Ltd.) were admixed at a ratio of 1:99 and solidified and then the spore suspension was inoculated at about  $10^5$  spores/ml. Cultivation was conducted at 28°C for 5 days and any growth of the fungus was confirmed.

[0042] The DMSO concentration was maintained at 1% or less so as not to affect the spore germination.

(5) Evaluation and calculation equation

[0043] Evaluation of a synergistic effect was made by calculating FIC index (Fractional Inhibitory Concentration index) from the minimum concentration of the composition (MIC: The minimum inhibitory concentration,  $\mu\text{g}/\text{ml}$ ), at which any growth of a microorganism was not observed at the end of the cultivation.

$$\text{(Calculation equation) FIC index} = a/a_0 + b/b_0$$

a: MIC of miconazole nitrate when used together with the test agent

$a_0$ : MIC of miconazole nitrate alone

b: MIC of the test agent when used together with miconazole nitrate

$b_0$ : MIC of the test agent alone

(Evaluation) Combined effect of the test agents was evaluated according to the following ratings:

>2	Antagonism
Not more than 2 - more than 1	Addition
Not more than 1	Synergism

(6) Results

[0044] The rating of not more than 1.0 was defined to demonstrate the development of synergism, taking into consideration the facts that the FIC index value for determining any synergism is to evaluate a bacteriostatic action and that this test is a primary screening. As a result, almost all test agents were established to show an additive or synergistic effect as shown in Table 2.

Table 2

Name of compound	FIC index	
	T. rubrum	T. mentagrophytes
Benzethonium chloride	0.49	0.55
Benzalkonium chloride	0.12	0.26
Dequalinium chloride	0.47	0.68
Salicylic acid	0.44	0.72

## Test Example 2

## (1) Test strains

[0045] The following microorganisms were used as test strains:

Trichophyton rubrum

Trichophyton mentagrophytes

## (2) Preparation of spore suspension

[0046] It was prepared in the same manner as described in Test Example 1.

## (3) Preparation of test compositions

[0047] Test compositions were prepared by using miconazole nitrate, econazole nitrate (comparative), clotrimazole (comparative) or bifonazole and dequalinium chloride, dissolving them and developed not only in case of miconazole nitrate but also the whole imidazole-type antifungal compounds.

## Test Example 3

## (1) Test strains

[0048] The following microorganisms were used as test strains:

Trichophyton rubrum

Trichophyton mentagrophytes

## (2) Preparation of spore suspension

[0049] It was prepared in the same manner as described in Test Example 1.

## (3) Preparation of test compositions

[0050] Test compositions were prepared by using miconazole nitrate (MCZ) and salicylic acid (comparative), benzalkonium chloride (BAC) (comparative) or dequalinium chloride (DQ), dissolving and then preparing doubling dilutions with DMSO as a dilution solvent so as to correspond to the test concentrations.

## (4) Test procedure

[0051] To 20 ml of 20 mM phosphate buffer (pH 6.5) sterilized by filtration was added and admixed 100  $\mu$ l each of the test compositions and then the spore suspension was added so as to be  $10^5$  spores/ml (usually 50 - 200  $\mu$ l) followed by stirring. While incubated at 30°C, the number of surviving spores was measured on day 0, 1, 2 and 3 after testing, respectively.

[0052] In this connection, the DMSO concentration was maintained at 1% or less so as not to affect the spore germination.

## (5) Measurement of number of surviving spores

[0053] The number of surviving spores in the spore suspension and the test solution was measured by preparing 10 times dilutions using sterile physiological saline or LP dilution liquid (DAIGO), smearing 50 µl each of the diluted liquids onto the Sabouraud's agar medium (Eiken Chemical Co., Ltd.) previously prepared, cultivating the medium at 28°C for 4 days or more in the case of *T. rubrum* or for 3 days or more in case of *T. mentagrophytes*, and then calculating the number of surviving spores in the spore suspension or the test solution from the number of the colonies as grown.

## (6) Evaluation of synergism

[0054] In accordance with the literature (Antimicrobial Agents and Chemotherapy, Feb. 1977, pp. 225-228), the test compositions were evaluated as synergistic, if a difference between the number of surviving spores when used alone and that of surviving spores when used in combination is of about 2 or more orders.

## [Test results]

## (1) Fungicidal activity curve of miconazole nitrate

[0055] The fungicidal activity of miconazole nitrate alone was determined in sterile physiological saline (pH 6.5). As a result, the fungicidal activity was potentiated in a concentration-dependent manner as shown in Fig. 1. The test for the combined effect was made at a selected concentration of 3.13 µg/ml, at which a synergistic fungicidal activity can be easily evaluated.

## (2) Fungicidal activity curve when used together with agents

[0056] The maximum blending ratios within the criterion of each agent to miconazole nitrate are shown in Table 4.

Table 4

Name of compound	Blending ratio*
Salicylic acid	10
Benzalkonium chloride	1
Dequalinium chloride	0.5

\*) when an amount of the miconazole nitrate to be blended is defined as 1

[0057] The fungicidal activity when used in combination was confirmed by adding each agent at the maximum blending ratio to 3.13 µg/ml of miconazole nitrate.

[0058] As shown in Fig. 2, it has been confirmed that the fungicidal activity when used in combination was much more potentiated than that of miconazole alone, except for the case of salicylic acid.

[0059] The effect of each agent was studied in detail as follows:

[0060] The effect by salicylic acid is illustrated in Fig. 3.

[0061] No fungicidal activity was observed when salicylic acid was used alone, while the fungicidal activity in combined use was equal to or less than that of miconazole nitrate alone. In view of the results of the FIC index from the primary screening, it is also assumed that the combined effect of salicylic acid may be of a bacteriostatic one.

[0062] The effect by benzalkonium chloride is illustrated in Fig. 4.

[0063] When benzalkonium chloride was used alone, the fungicidal activity was of the same level as miconazole nitrate in case of *T. rub.* or of the higher level than that of miconazole nitrate in case of *T. menta.*, while the fungicidal activity in the combined use was less than the detection limit in both fungi on day 1.

[0064] The effect by dequalinium chloride is illustrated in Fig. 5.

[0065] The fungicidal activity of dequalinium chloride alone was equal to that of miconazole nitrate alone and was less than the detection limit when used in combination on day 2.

[0066] In accordance with the literature (Antimicrobial Agents and Chemotherapy, Feb. 1977, pp. 225-228), synergism in fungicidal activity is evaluated effective if a difference in the number of surviving spores is of 2 or more orders between the single use and the combined use. Therefore, benzalkonium chloride and dequalinium chloride have been evaluated to exert a synergistic fungicidal activity.

## Test Example 4

## (1) Test strains

5 [0067] The following microorganisms were used as test strains:

Candida albicans

Staphylococcus aureus

10 (2) Preparation of microbial suspension

[0068] Candida albicans was cultivated on Sabouraud's agar medium (Eiken Chemical Co., Ltd.) at 28°C for 24 hours and then suspended in sterile physiological saline so as to form a microbial suspension of about  $10^6$ /ml.

15 [0069] Staphylococcus aureus was cultivated on Mueller-Hinton agar medium (Eiken Chemical Co., Ltd.) at 37°C for 18 hours and then suspended in sterile physiological saline so as to form a microbial suspension of about  $10^6$ /ml.

(3) Preparation of test compositions

20 [0070] Test compositions were prepared by using miconazole nitrate and dequalinium chloride, dissolving them and then preparing doubling dilutions with DMSO as a dilution solvent so as to correspond to the test concentrations.

(4) Test procedure

25 [0071] The diluted composition and Sabouraud's agar medium (Eiken Chemical Co., Ltd.) were admixed at a ratio of 1 : 99 and solidified and then the microbial suspension of Candida albicans was inoculated. Cultivation was conducted at 30°C for 2 days and any growth of the fungus was confirmed.

[0072] The diluted composition and Mueller-Hinton agar medium (Eiken Chemical Co., Ltd.) were admixed at a ratio of 1 : 99 and solidified and then the microbial suspension of Staphylococcus aureus was inoculated. Cultivation was conducted at 30°C for 24 hours and any growth of the bacterium was confirmed.

30

(5) Evaluation and calculation equation

[0073] Calculation and evaluation were performed in the same manner as described in Test Example 1.

35 (6) Results

[0074] The results are shown in Table 5.

Table 5

40

Test strain	FIC index
<u>Candida albicans</u>	0.11
<u>Staphylococcus aureus</u>	0.75

45 [0075] Synergism by a combination of miconazole nitrate with dequalinium chloride was also observed against Candida albicans and Staphylococcus aureus.

Test Example 5

50 [0076] Influence by blending ratios (1 : 0.12 - 1.00) of miconazole nitrate and dequalinium chloride were studied following the same test procedure as described in Test Example 3 and the results are shown in Fig. 6.

[0077] As a result, blending ratio of 1 : 0.12 or more gave a much more potent fungicidal activity than that of miconazole nitrate alone or dequalinium chloride alone and synergism was also observed.

55 Test Example 6 Influence of lecithin

[0078] Lecithin, which has been employed as a base for creams, is known to be an inactivating agent for fungicides such as quaternary ammonium salts and the like [Tadaichi ISHIZEKI et al., the Journal of the National Institute of

Hygienic Sciences, No. 91 (1973)], and its influence on synergism of miconazole nitrate with dequalinium chloride was studied.

[0079] The same test procedure as described in Test Example 3 was repeated with a lecithin concentration which was adjusted to a blending ratio (miconazole nitrate : lecithin = 1 : 0.5) in case of miconazole nitrate alone, or with a lecithin concentration of 1.57 µg/ml when dequalinium chloride was used alone or in combination with miconazole nitrate.

[0080] As a result, no influence was observed at these concentrations.

#### BEST MODE FOR CARRYING OUT THE INVENTION

[0081] This invention will be explained in detail by the following examples.

##### Example 1

(Example of Formulation for Creams)

[0082]

Miconazole nitrate	100 g
Lidocaine	200 g
Dequalinium chloride	10 g
Polyoxyethylene sorbitan monostearate	400 g
Sorbitan monostearate	200 g
1,3-Butylene glycol	1,500 g
Medium chain fatty acid triglyceride	1,500 g
Glyderol monostearate	250 g
EDTA-2Na	10 g
Purified water	q.s. to a total of 10,000 g

(Preparation)

[0083] To aqueous phase components (1,3-butylene glycol, EDTA-2Na, dequalinium chloride and purified water) were added oily phase components (miconazole nitrate, lidocaine, sorbitan monostearate, medium chain fatty acid triglyceride, glycerol monostearate and polyoxyethylene sorbitan monostearate), and the mixture was warmed to prepare 10,000 g of creams.

##### Example 2

(Example of Formulation for Solutions)

[0084]

Miconazole nitrate	100 g
Dequalinium chloride	20 g
Dipotassium glycyrrhizinate	50 g
BHT	5 g
Ethanol	5,000 g
Purified water	q.s. to a total of 10,000 ml

(Preparation)

[0085] In the ethanol were dissolved the other agents and the purified water was added to make up a total volume to 10,000 ml.



## Example 3

(Example of Formulation for Gel Creams)

[0086]

Miconazole nitrate	100 g
Dequalinium chloride	20 g
Lidocaine	200 g
Polyoxyethylene sorbitan monostearate	100 g
Propylene glycol	1,000 g
Liquid paraffin	500 g
Stearyl alcohol	100 g
Carboxyvinyl polymer	50 g
Diisopropanolamine	100 g
Purified water	q.s. to a total of 10,000 g

(Preparation)

Oily phase components (the miconazole nitrate, lidocaine, dequalinium chloride, polyoxyethylene sorbitan monostearate, liquid paraffin and stearyl alcohol) were dissolved by warming and allowed to cool to room temperature. Then, the carboxyvinyl polymer was dissolved in the water and the propylene glycol and allowed to stand at room temperature to make the carboxyvinyl polymer swollen. The said oily phase and aqueous phase were stirred at room temperature to prepare gel creams.

## Example 4

(Example of Formulation for Aerosols)

[0088]

Concentrate:	
Miconazole nitrate	50 g
Dequalinium chloride	5 g
Dipotassium glycyrrhizinate	25 g
Ethanol	2,500 g
Purified water	5,000 ml
Propellant:	
LPG	5,000 ml

(Preparation)

Main active ingredients were dissolved in a base composed of the ethanol and the water to form a stock solution, which was then charged into a container. A valve was fitted with the container, into which the propellant was then injected to prepare aerosols.

## BRIEF DESCRIPTION OF DRAWING

Fig. 1 graphically shows the fungicidal activity of miconazole nitrate against *T. rubrum* (A) and *T. mentagrophytes* (B). The number of storage days is plotted on the abscissa and a logarithm of the number of surviving fungi/ml is on the ordinate (That is, 1 means  $10^1$  spores/ml, 2 does  $10^2$  spores/ml, 3 does  $10^3$  spores/ml and 4 does  $10^4$  spores/ml).

Fig. 2 graphically shows the fungicidal activity of a combination of the antifungal compound with the agent against *T. rubrum* (A) and *T. mentagrophytes* (B). The number of storage days is plotted on the abscissa and a logarithm

of the number of surviving fungi/ml is on the ordinance. MCZ represents miconazole nitrate, BAC does benzalkonium chloride (comparative) and DQ does dequalinium chloride.

[0092] Fig. 3 graphically shows the fungicidal activity of the antifungal compound used together with salicylic acid (comparative) against *T. rubrum* (A) and *T. mentagrophytes* (B). The number of storage days is plotted on the abscissa and a logarithm of the number of surviving fungi/ml is on the ordinance. MCZ represents miconazole nitrate.

[0093] Fig. 4 graphically shows the fungicidal activity of the antifungal compound used together with benzalkonium chloride (comparative) against *T. rubrum* (A) and *T. mentagrophytes* (B). The number of storage days is plotted on the abscissa and a logarithm of the number of surviving fungi/ml is on the ordinance. MCZ represents miconazole nitrate and BAC does dequalinium chloride.

[0094] Fig. 5 graphically shows the fungicidal activity of the antifungal compound used together with dequalinium chloride against *T. rubrum* (A) and *T. mentagrophytes* (B). The number of storage days is plotted on the abscissa and a logarithm of the number of surviving fungi/ml is on the ordinance. MCZ represents miconazole nitrate and DQ does dequalinium chloride.

[0095] Fig. 6 graphically shows the results from studies on influence upon the blending ratio of miconazole nitrate with dequalinium chloride. The number of storage days is plotted on the abscissa and a logarithm of the number of surviving fungi/ml is on the ordinance. MCZ represents miconazole nitrate.

## Claims

1. Composition comprising (A) miconazole nitrate or bifonazole and (B) dequalinium chloride for use as a medicament acting against fungi of Trichophyton and Candida.
2. The composition of claim 1, comprising (A) miconazole nitrate or bifonazole in an amount to be blended of 0.2 - 1% by weight and (B) dequalinium chloride in an amount to be blended of 0.1 - 1% by weight.
3. The composition of claim 1, wherein 0.1 - 1 part by weight of (B) dequalinium chloride has been blended per 1 part by weight of (A) miconazole nitrate or bifonazole.
4. Use of a composition which comprises (A) miconazole nitrate or bifonazole and (B) dequalinium chloride for the manufacture of a medicament acting against fungi of Trichophyton and Candida.
5. The use of a composition as claimed in claim 4, wherein said composition comprises (A) miconazole nitrate or bifonazole in an amount to be blended of 0.2 - 1% by weight and (B) dequalinium chloride in an amount to be blended of 0.1 - 1% by weight.
6. The use of a composition as claimed in claim 4, wherein 0.1 - 1 part by weight of (B) dequalinium chloride has been blended per 1 part by weight of (A) miconazole nitrate or bifonazole.

## Patentansprüche

1. Zusammensetzung, umfassend (A) Miconazolnitrat oder Bifonazol und (B) Dequaliniumchlorid, die zur Verwendung als Medikament gegen Trichophyton- und Candida-Pilze wirksam ist.
2. Zusammensetzung nach Anspruch 1, umfassend (A) Miconazolnitrat oder Bifonazol in einer Menge von 0,2 bis 1 Gew.-% und (B) Dequaliniumchlorid in einer Menge von 0,1 bis 1 Gew.-%.
3. Zusammensetzung nach Anspruch 1, **dadurch gekennzeichnet**, dass 0,1 bis 1 Gew.-Teil (B) Dequaliniumchlorid je 1 Gew.-Teil (A) Miconazolnitrat oder Bifonazol eingesetzt werden.
4. Verwendung einer Zusammensetzung, die (A) Miconazolnitrat oder Bifonazol und (B) Dequaliniumchlorid umfasst, zur Herstellung eines Medikaments, das gegen Trichophyton- und Candida-Pilze wirksam ist.
5. Verwendung einer Zusammensetzung nach Anspruch 4, **dadurch gekennzeichnet**, dass die Zusammensetzung (A) Miconazolnitrat oder Bifonazol in einer Menge von 0,2 bis 1 Gew.-% und (B) Dequaliniumchlorid in einer Menge von 0,1 bis 1 Gew.-% umfasst.

6. Verwendung einer Zusammensetzung nach Anspruch 4, **dadurch gekennzeichnet**, dass 0,1 bis 1 Gew.-Teil (B) Dequaliniumchlorid je 1 Gew.-Teil (A) Miconazolnitrat oder Bifonazol eingesetzt werden.

5    **Revendications**

1. Composition comprenant (A) du nitrate de miconazole ou du bifonazole et (B) du chlorure de déqualinium, destinée à une utilisation en tant que médicament agissant contre les champignons *Trichophyton* et *Candida*.
- 10    2. Composition selon la revendication 1, comprenant (A) du nitrate de miconazole ou du bifonazole en une quantité à mélanger de 0,2 - 1 % en poids et (B) du chlorure de déqualinium en une quantité à mélanger de 0,1 - 1 % en poids.
3. Composition selon la revendication 1, dans laquelle on mélange 0,1 - 1 partie en poids de (B) chlorure de déqualinium pour 1 partie en poids de (A) nitrate de miconazole ou bifonazole.
- 15    4. Utilisation d'une composition comprenant (A) du nitrate de miconazole ou du bifonazole et (B) du chlorure de déqualinium pour la fabrication d'un médicament agissant contre les champignons *Trichophyton* et *Candida*.
- 20    5. Utilisation d'une composition selon la revendication 4, ladite composition comprenant (A) du nitrate de miconazole ou du bifonazole en une quantité à mélanger de 0,2 - 1 % en poids et (B) du chlorure de déqualinium en une quantité à mélanger de 0,1 - 1 % en poids.
- 25    6. Utilisation d'une composition selon la revendication 4, dans laquelle on mélange 0,1 - 1 partie en poids de (B) chlorure de déqualinium pour 1 partie en poids de (A) nitrate de miconazole ou bifonazole.

FIG. 1

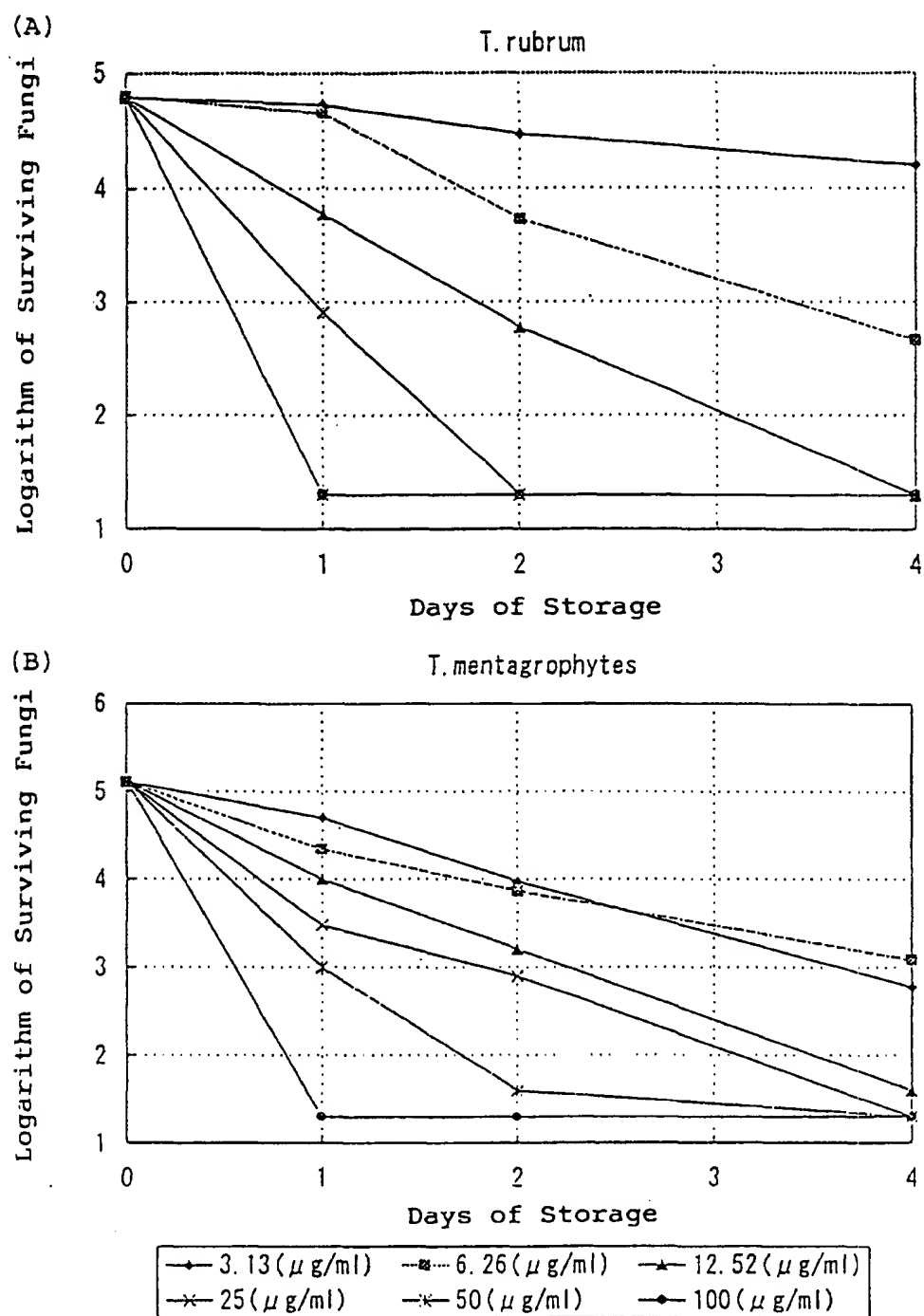


FIG. 2

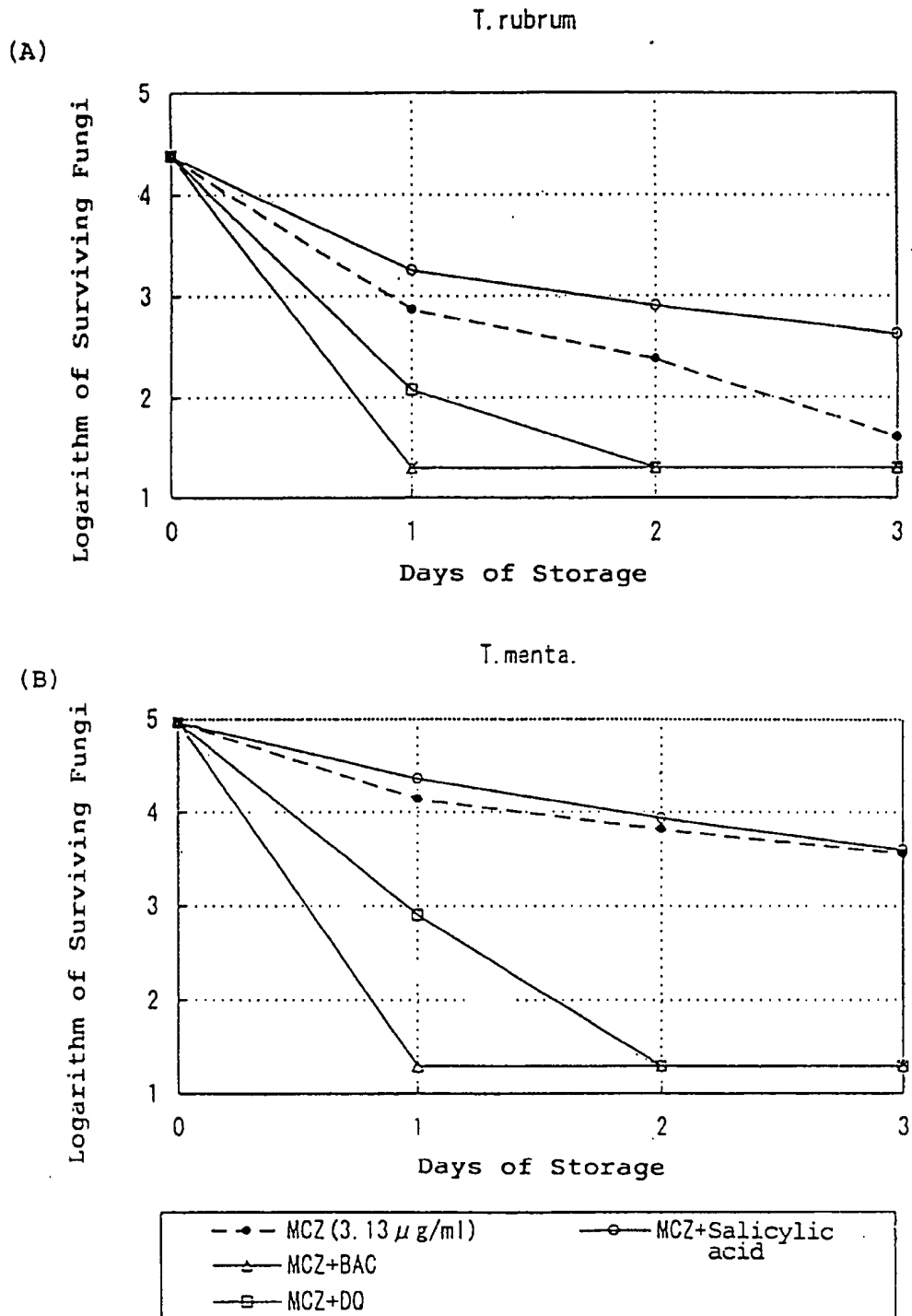


FIG. 3

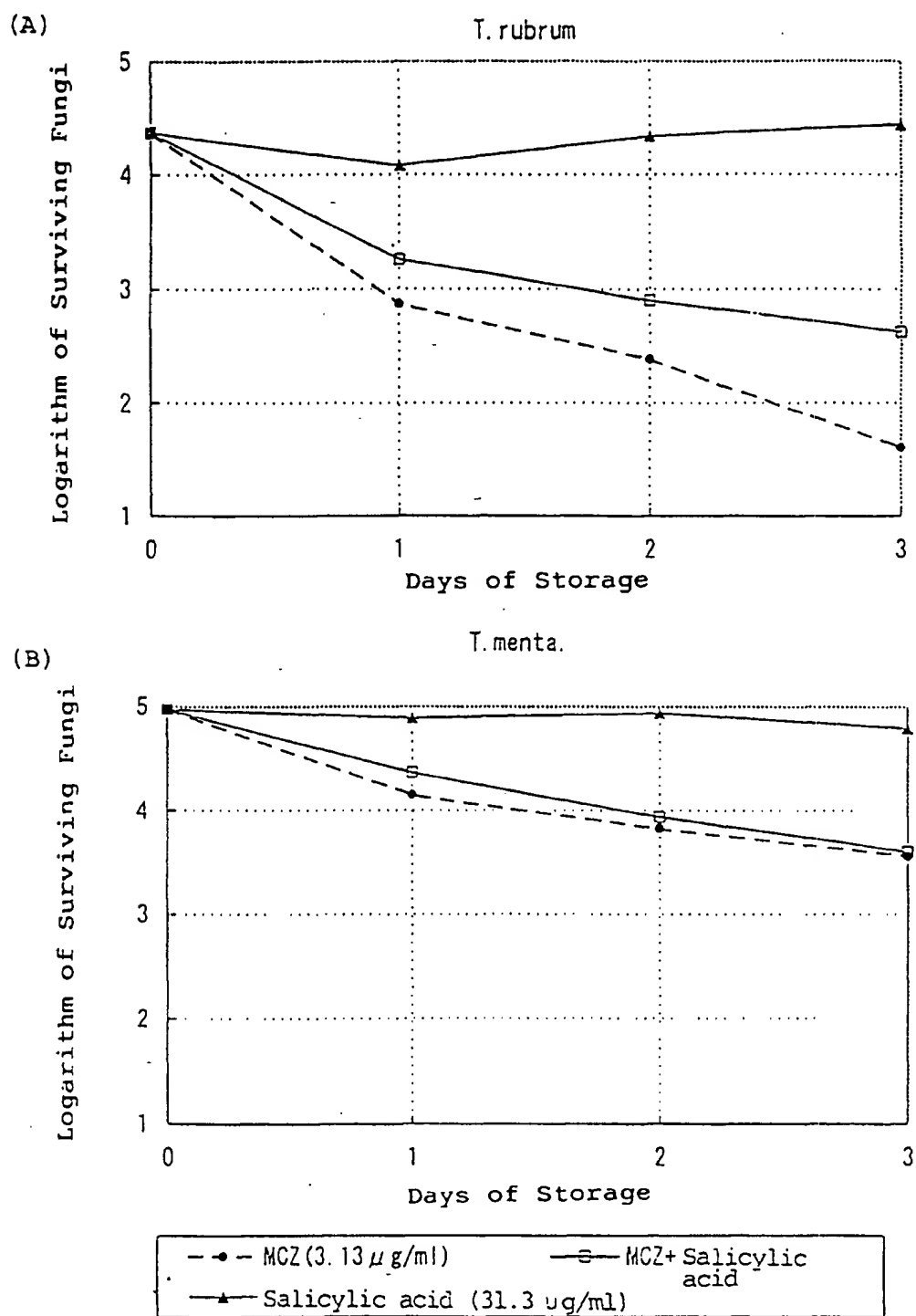


FIG. 4

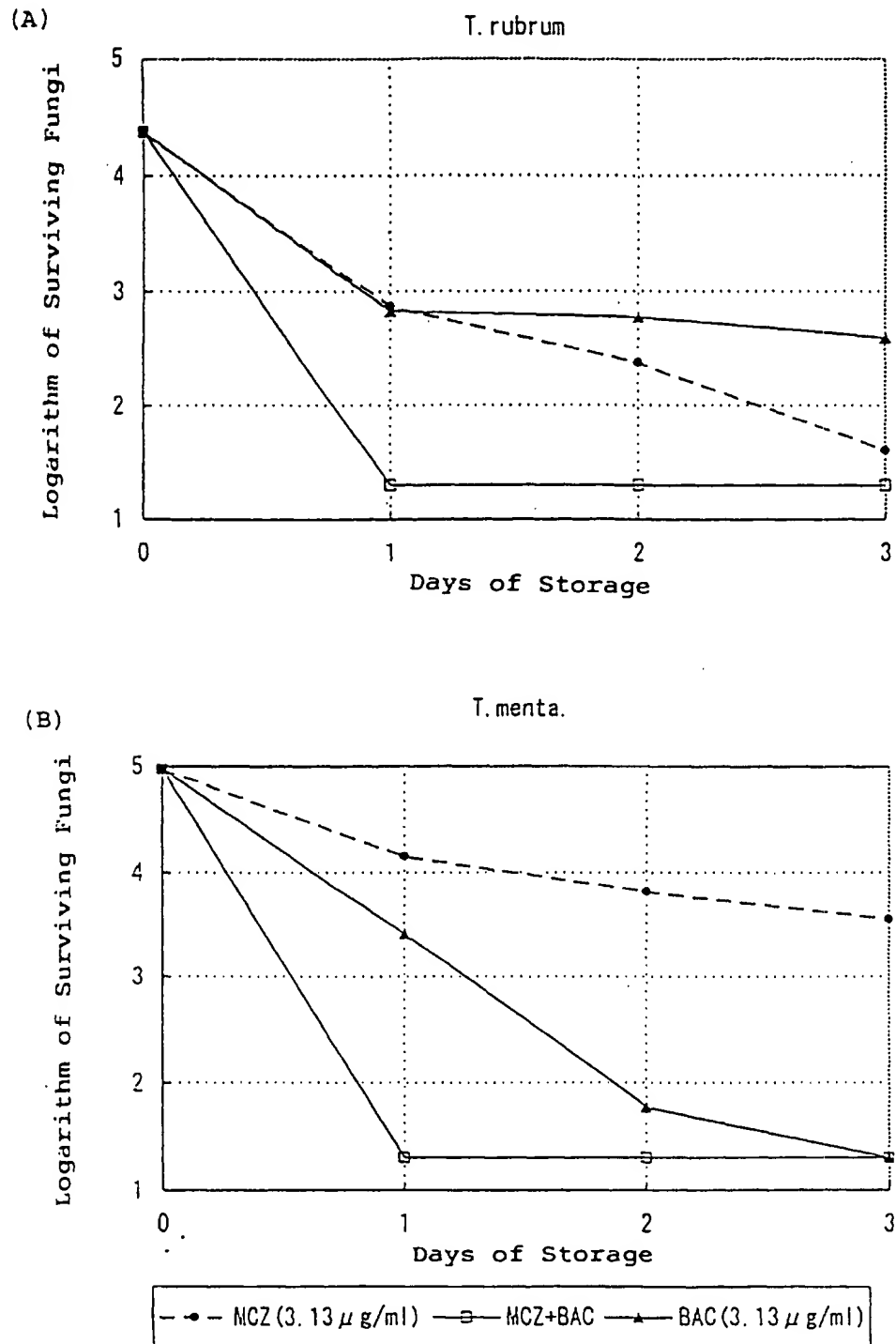


FIG. 5

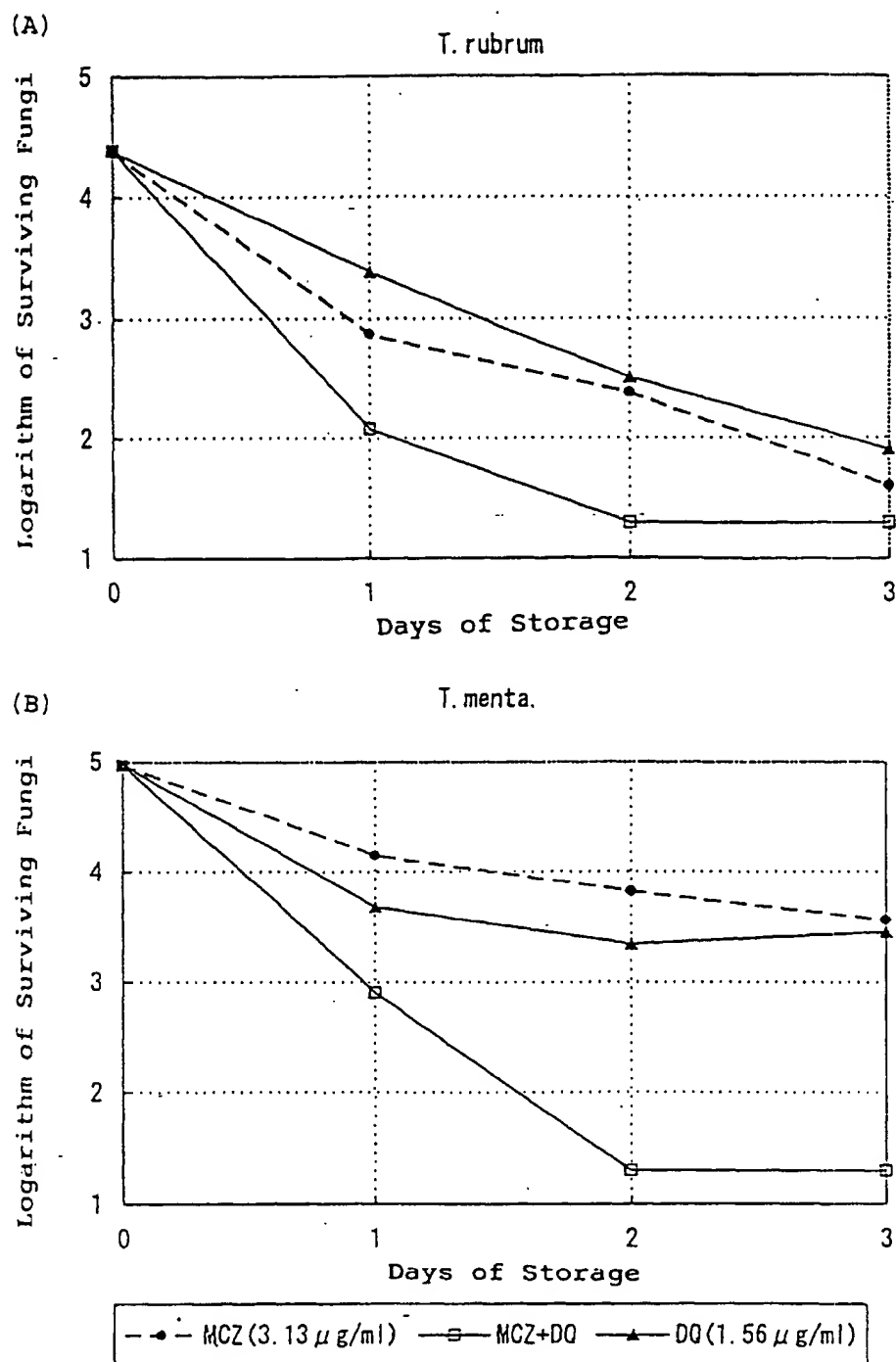




FIG. 6

